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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/064,057	04/22/1998	GARY F. GERARD	0942.4330002	5386

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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	49

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/064,057	Applicant(s) Gerard et al.
	Examiner Nashaat T. Nashed	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 21, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26, 28, 33, 117-125, and 127-151* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26, 28, 33, 117-125, and 127-151* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 21, 2003 has been entered.

The application has been amended as requested in the communication filed July 21, 2003. Accordingly, claims 26, 28, 117-125, and 127-148 have been amended and new claims 149-151.

Claims 26, 28, 33, 117-125, and 127-151 are pending and under consideration in this Office action.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures for the reasons set forth in the prior Office action, paper number 41.

In response to the above objection to the specification, applicants argue that applicants need not disclose art known or standard amino acid sequences or the position of conserved residues.

Applicants' arguments filed 7/21/03 have been fully considered, but they are not deemed to be persuasive. While it is applicants need not disclose known art, applicant must write their specification in clear and understandable manner wherein all important subject matter are identified. Applicant should be reminded that all lenta viruses are highly mutagenized in the wild. Thus, a known reverse transcriptase may have a specific amino acid residue at its specified position or not. Without identifying a specific amino acid sequence, at least to reference the numbering system for the amino acid, one of ordinary skill in the art would not be able to understand the specification. The specification discusses several specific mutants of some reverse transcriptase at specific amino acid residues without identifying the amino acid sequence from which those residues are from. For example on page 57, the text indicates the mutation of Asp-450 to Ala, Glu-484 to Gln, and Asp-505 to Asn, presumably, from an RSV-reverse transcriptase without identifying the amino acid sequence by a sequence identification number. Another examples of improper disclosure of specific amino and nucleic acid sequences is found on page 73, lines 13-15. Referencing a specific amino/nucleic acid sequence by an accession number

in commercial data base is improper since the data base may change the accession number without referencing the old number. Thus, the specification fails to comply with the sequence rule. Applicants are required to perfect their compliance with the sequence rules.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28, 33, 117-125, and 127-151 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons set forth in the prior Office actions, papers numbers 41 and 45.

Applicants argue that: (1) the they are enclosing a copy of a declaration concerning deposits of biological material, filed in copending application 09/245,026 obviating the rejection; (2) Johnson *et al.* teach the alignment of RSV, M-MLV, and HIV and show that reverse transcriptase have significant conservation between a 150- residue segment in their carboxyl termini; (3) Grandgenett et al. showed that AMV reverse transcriptase is active in the monomeric α form; and (4) the specification has described βp4 subunit, see page 4, lines 22-28 and page 56, lines 12-14.

Applicants' arguments filed 7/21/03 have been fully considered, but they are not deemed to be persuasive. The following are the reasons for maintaining the rejection:

(1) The amendment does not contain a copy of said declaration. When the applicant file the copy of the declaration, the examiner will consider it as it relate to this rejection.

(2) This rejection is for lack of written description and not for lack of enablement. So applicant can not relay on the prior art in describing their own invention. Even the cited prior by the applicants does not teach RnaseH domain of AMV-RT. According to the applicants, Johnson *et al.* identified residues D450, Q481, E483, L492, N501, D505, S506, H549, 560, and D564, presumably, numbered according to one or another RSV-RT amino acid sequence. Clearly, it appears that the applicants could not find a description of the RnaseH domain in the specification or the prior.

(3) The examiner have examined Grandgenett et al. They teach a protein preparation comprising the α-subunit having RNA-dependent DNA-polymerase and RnaseH activities. There are no part of the paper indicating that the observed activity is from the monomeric form of the α-subunit. Based on more recent prior art, e. g., Soltis *et al.*, it is known that both the homodimeric form of the enzyme have polymerase activity.

(4) The examiner disagrees with regard of the written description of the βp4 subunit because the specification does not describe said subunit by any structural or chemical features by which it can be identified.

Thus, the above rejection are maintained for the reasons set forth above. New claim 149-151 are included in this rejection because they are dependent on a rejected claim and do not obviate its deficiencies.

Claims 28, 33, 117-121, 124, 125 and 127-151 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, see the previous Office actions, papers numbers 41 and 45. The following are the reasons for the rejections:

(a) The phrase and "one or more subunits" in claims 28 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. One or more subunit is considered indefinite because the enzymatically active form of the enzyme is a dimer and therefore there could not be more than two subunits per molecule of enzyme. For examination purposes only, "one or more subunits" is assumed to mean homo dimer containing two α-AMV reverse transcriptase or two β-AMV reverse transcriptase; or heterodimer containing one of each the α- and β-subunits of AMV reverse transcriptase.

Applicant traverse the above rejection on the ground that monomeric α-subunit has enzymatic activity.

Applicants' arguments filed 7/21/03 have been fully considered but they are not deemed to be persuasive. The examiner disagrees with the applicants reading of the cited article. As indicated above, the article teach a preparation containing α-subunit which displays enzymatic activity. Both homodimeric AMV-RT are known to have enzymatic activity, see Soltis *et al.*

(c) the phrase "βp4 subunit" in claim 28, 120, and 148 is not structurally defined by the specification or the claim, and therefore, the claim is considered indefinite. For examination purposes, the phrase is interpreted as a mutant

or naturally occurring allelic variants of the β-subunit which has a reverse transcriptase activity.

Applicant traverse the above rejection on the ground that βp4 subunit is defined on page 4, line 23-26, and page 56, and reiterated their previous arguments.

Applicants' arguments filed 7/21/03 have been fully considered but they are not deemed to be persuasive. Page 4, lines 23-26 teach the conversion of a 98 kDa polypeptide precursor which is converted to mature β-subunit and a p4 polypeptide. While the β-subunit of AMV-RT is well known and therefore is well defined and has enzymatic activity as a homo- and heterodimer with the α-subunit, the p4 polypeptide is not known to have any enzymatic activity as a homo- or heterodimer. This particular argument further confuses the meaning and the chemical structure of the "βp4-subunit". On page 56, the phrase AMV-RT does not appear once, and the "βp4-subunit" appears to mean the polypeptide precursor which produces the β-subunit. It is well established that α-subunit is formed from a polyprotein precursor from which the β-subunit is obtained by proteolytic cleavage. Does that make "βp4-subunit" identical to the α-subunit?

(d) Claims 117-119, 121, 124, 125, 127-147, and 149-151 are included in these rejection because they are dependent from rejected claims and do not correct their deficiencies.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under

37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 26, 28, 33, 117-119, 121-125 and 127-151 are rejected under 35 U.S.C. § 103 as being unpatentable over Soltis *et al.* in view of the state of the art at the time of the application was filed.

In response to the above rejections, Applicants limited the claims to a recombinant method using eukaryotic host cell and argue that: (1) one of ordinary skill in the art would have had no motivation of producing AMV-reverse transcriptase by a recombinant method because the enzyme was satisfactorily produced from its virus with a specific activity of >50,000 units per milligram; (2) one of ordinary skill in the art would not have had expectation of success because of the teaching of, presumably, Prasad *et al.*, a review article, published in 1993; (3) applicants cites several articles in the prior art, all of which published in or prior to 1993, describing the expression of HIV-RT in insect cells and yeast cells, and compare the specific activities of the enzyme expressed in said cells and a preparation obtained from the expression in *E. coli* showing the specific activity of the enzyme expressed in *E. coli* is higher those expressed in yeast and insects cells; and (4) applicants provide Gerard *et al.* (copy of the reference is not provided) which describe the production and purification of the AMV-RT in insects cells with a specific activity of 57,500 units/mg, presumably, of protein.

Applicants' arguments filed 7/21/03 have been fully considered but they are not deemed to be persuasive. The ordinary skill in the art indeed would have had motivation and expectation of success to develop a recombinant method to obtain AMV-RT in large quantities. As pointed out by the applicants, AMV-RT is widely used in biotechnology and is produced by purification from cultured virus. With the expanding of biotechnology, the need for reliable source of the enzyme in large quantities would have motivated one of ordinary skill in the art at the time of invention to develop a recombinant method to obtain the enzyme. In fact, Soltis *et al.* have developed such a method in *E. coli* which provide a *prima facie* evidence for the expectation of success in developing a recombinant methods for the production of AMV-RT. Now, the claims are limited to a method of making AMV-RT utilizing a eukaryotic host cells. Yeast is a common eukaryotic host cells which is used routinely in many recombinant method to produce proteins and enzymes including other reverse transcriptases, *vida infra*. Applicants have cited several article published in and prior to 1993 which describes the expression of HIV-RT in insects and yeast cells (Kawa *et al.* and Barr *et al.*, respectively) as well as in *E. coli* (Lowe *et al.*). The three articles clearly show that a reverse transcriptase can be recombinantly produced in eukaryotic host cells and *E. coli* having the desired enzymatic activities. There are two

reasons for one of ordinary skill in the art to reject the improper activity comparison made by the applicants. First, Barr *et al.* presented their results as units of activity at a given concentrations of a the template/template and TTP (136.5 μM). In contrast, Lowe *et al.* presented a V_{max} obtained from nonlinear fit of V= V_{max} S/Km + S at a constant concentration of the template/ primer and varied the concentration dTTP, without reporting the concentration of the template/primer. Also, it should be pointed out that dTTP displays a substrate inhibition at concentration about 100 μM of dTTP. Second, one of ordinary skill in the art would have expected that the specific activity of a purified protein is related to its method of purification and not to the host cell used in its expression. Since the argument presented by the applicants would not hold for HIV-RT, it would not be applicable to AMV-reverse transcriptase. In contrast, both Kawa *et al.* and Barr *et al.* support the rejection of the claims under 35 U.S.C. § 103 as they teach the expression of a reverse transcriptase recombinantly produced in eukaryotic host cells. Both articles provide one of ordinary skill in the art with a motivation at the time of invention to express the AMV-RT in eukaryotic cell as they teach that eukaryotic cells have the pathways that facilitate folding, modification, and assembly of protein products, Kawa *et al.*, page 302, the paragraph bridging the left and right columns; and Barr *et al.* page 486, the paragraph bridging the left and right columns. In addition, one of ordinary skill in the art would expect that an AMV-RT produced by a method involving the expression of AMV-RT as a fusion protein such as AMV-RT-6His fusion protein would yield AMV-RT with the highest possible activity. Applicants should be reminded that between 1993 and 1997 there has been great improvements in biotechnology and expression of proteins and enzymes in various host cells. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious, and therefore the claims remain rejected. New claims 149-151 are included in this rejection because they are dependent on claim 26 and define the host cell as insect cell, insect larva cell and yeast cell. Finally, it appears that the applicants could not produce and purify the AMV-RT from transformed insects cells with a specific activity of greater than 57,500 units/mg of protein, presumably, their best effort. Why would they expect a better results from their own method according to claims 127-137 and 143-147?

No claim is allowed.

This is a RCE of applicant's earlier Application No. 09/064,057. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner